REMARKS/ARGUMENTS

After entry of this paper, claims 2, 3, 5, 6, 21, 23, and 43-59 are pending. Claims 1, 4, 7-20, 22, and 24-42 are canceled, without prejudice. Applicants reserve the right to prosecute any previously or currently canceled claims or subject matter in a divisional or continuation application filed during the pendency of the present application.

Claims 2, 3, 5, and 6 are amended to provide the full isolated nucleic acid sequence of SEQ ID NO: 1 or a sequence complementary thereto. The subject matter of sections (b)-(e) canceled from claim 2 is incorporated into new claims 44-46 and 59.

As amended, claims 21 and 23 and new claims 43-48, recite reagents useful for detecting expression of the wild-type *chfr* gene or a mutation in the *chfr* gene in a cell. The reagents include a nucleic acid sequence 12-30 nucleobases in length that is complementary or identical to a portion of SEQ ID NO: 1. Support for the amendments to claims 21 and 23 and new claims 43-48 is found in the original specification on page 5, lines 3-10; page 17, lines 28-30; page 23, lines 19-24; page 28, lines 3-4; and page 45, lines 21-22.

New claims 49-58 are drawn to kits containing fragments of the nucleotide sequence of SEQ ID NO: 1 that are 12-30 nucleotides in length and bind to *chfr*. The kits are useful for determining expression of the wild-type *chfr* gene or a mutation in the *chfr* gene. Specifically, the kits are useful for detecting the sensitivity of cancer cells to anti-mitotic drugs, including the Taxol® agent. Support for these new claims is found in the original specification on page 9, lines 9-14; page 13, lines 13-15; page 17, lines 13-30; page 22, lines 5-22; page 23, lines 19-24; and page 28, lines 3-4.

New claims 43 and 51-53 provide reagents or kits containing detectable labels. Support for these claims is found in the original specification on page 21, lines 1-27.

New claims 47, 56, and 57 provide the use of the reagents or kits of the present application in PCR assays, which claims are fully supported on page 24, lines 18-29 of the original specification.

No new matter is added by these claim amendments and new claims which are presented to clarify the invention.

Information Disclosure Statement

Applicants submit herewith a Third Information Disclosure Statement. Applicants respectfully request that the Examiner consider the documents cited therein during prosecution of this application.

Claim Objections

(i) *Claims 1, 21, 23, and 25 are objected to for the term "associated". Claims 21 and 23 are further objected to for the term "diagnostic agent".*

The cancellation of claims 1 and 25 moots the outstanding objection as applied to these claims.

Claims 21 and 23 were amended to remove the objected terms "associated" or "diagnostic". Further, the remaining amended and newly added claims that are not subject to this rejection do not contain the allegedly objectionable terms "diagnostic" or "associated".

Reconsideration of this objection is requested.

(ii) *Claims 23, 25, 27, 31, and 32 are objected to for containing non-elected subject matter drawn to a "polypeptide ligand which binds to Chfr" and "...an inhibitor which is not a polynucleotide or antisense inhibitor...".*

The cancellation of claims 25, 27, 31, and 32 moots the outstanding objection as applied to these claims.

Claim 23 is amended to depend from claim 21, which does not include any non-elected subject matter drawn to polypeptides. Nor does amended claim 23 contain subject matter drawn to "an inhibitor which is not a polynucleotide or antisense

inhibitor". The remaining amended and newly added claims also do not contain the non-elected subject matter.

Reconsideration of this objection is requested.

35 USC § 112, First Paragraph, Written Description Rejection

Claims 21-23 and 25 are rejected under 35 USC § 112, first paragraph.

The Examiner asserted that the specification does not describe (i) a nucleotide sequence which "binds" to the chfr nucleic acid sequence and is an antisense fragment of SEQ ID NO: 1, or a ligand that binds to chfr or the chfr nucleic acid sequence, (ii) the complete structure of (i); (iii) any partial structure of (i); or (iv) any physical or chemical characteristics of (i). (pages 7-8 of Office Action) The Examiner also asserted that the specification does not describe a representative number of nucleotide sequences or "structural features common to the members of the genus, which features constitute a substantial portion of the genus". (page 8 of Office Action)

The Examiner further asserted that there is no limitation as to the nature of the molecules attached to an antisense fragment or a fragment of SEQ ID NO: 1 and that the present claim encompasses full-length genes and cDNAs that are not further described. (page 4 of Office Action)

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

Claims 22 and 25 are canceled, thereby mooting the outstanding rejection as applied to these claims.

The remaining claims are fully supported by the specification as illustrated by the specific portions of the specification noted above and set forth below.

Amended claims 21, 23, and 43-58 are drawn to reagents and kits containing nucleic acid sequences 12-30 nucleobases in length (page 17, line 30). The sequences are complementary (page 9 line 23 through page 10, line 6) or identical (page 12, lines 24-28) to selected portions of SEQ ID NO: 1. The reagents are useful for detecting expression of the wild-type *chfr* gene or a mutation in the *chfr* gene in a cancer cell (page 5, lines 5-7). The detection of the expression of the wild-type *chfr* gene or a mutation therein is useful for detecting the sensitivity of a mammalian subject to anti-mitotic drugs

(page 45, lines 21-22). The specification provides the Taxol® agent as an anti-mitotic drug (throughout Example 4 and specifically on page 45, lines 21-22).

Amended claim 23 and new claim 43 further provide labels that can be used with the nucleic acid sequences of the present invention (page 20, line 28 through page 21, line 27).

New claims 44-46 and 59 provide specific nucleotide sequences that are 12-30 nucleobases in length and that encode amino acids 31-103, 303 to 346, or 476 to 641 of SEQ ID NO: 2 (page 13, lines 14-15) and the use of the same in the present invention. This language is also fully supported by the original claim 2, which language forms part of the originally filed specification.

New claim 50 provides analyzing tumor cells for one or more characteristics (page 24, lines 6-11 and original claims).

Finally, the specification provides support for sequences that are complementary to the nucleotide sequences of the present invention (page 17, line 28 through page 18, line 6). However, one with even rudimentary skill in the art would be able to prepare sequences complementary to SEQ ID NO:1 and fragments thereof without undue experimentation.

Applicants therefore assert that the specification fully supports the amended and new claims and request reconsideration of this rejection.

35 USC § 112, First Paragraph, Enablement Rejections

(i) *Claims 1-6, 21-23, 25, 27, and 32 are rejected under 35 USC § 112, first paragraph.*

The Examiner asserted that the specification does not support (a) a nucleic acid sequence of a mitotic checkpoint gene encoding a chfr protein having a Forkhead-associated domain, and a Ring finger, where the protein is required for regulation of the transition of cells from prophase to metaphase, (b) the sequence encoding at least AA 31-103, 303-346, 476-641 of SEQ ID NO: 2 or combinations thereof, (c) a sequence at least 50% homologous to SEQ ID NO: 1, (d) the sequence encoding at least AA 31-103, 303-346, 476-641 of SEQ ID NO: 2 or combinations thereof using a selected algorithm and encoding a protein or peptide having ubiquitin-

protein ligase activity, and (e) a nucleotide sequence or a ligand which binds to the chfr nucleic acid sequence, or a fragment thereof, and which is an antisense fragment of SEQ ID NO: 1 or a fragment thereof.

(ii) Claim 25 is rejected under 35 USC § 112, first paragraph.

The Examiner asserted that the specification does not support a kit for detecting the tumorigenic potential of a cell.

(iii) Claims 27 and 32 are rejected under 35 USC § 112, first paragraph.

The Examiner asserted that the specification does not support a composition which inhibits the biological activity of chfr or an inhibitor of chfr.

(iv) Claims 1-5 are rejected under 35 USC § 112, first paragraph.

The Examiner asserted that the specification does not support a nucleic acid sequence encoding a chfr protein, where the protein is required for "regulation of the transition of cells from prophase to metaphase.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

Claims 1, 4, 22, 25, 27, and 32 are canceled, thereby mooting the outstanding rejection as applied to these claims.

Applicants respectfully disagree with the Examiner and assert that the original specification and claims ***fully enable*** the amended claims and new claims of this application. Applicants were the first to isolate and identify the *chfr* gene and sequence thereof. The sequence of the *chfr* gene is provided in Applicants' specification as SEQ ID NO: 1. Applicants also pointed to specific fragments of the same throughout the specification. Specifically, amended claims 2, 3, 5, and 6 and new claim 59 drawn to the nucleic acid sequence of SEQ ID NO: 1 and fragments thereof are enabled by the sequence provided in SEQ ID NO: 1. One of skill in the art would easily be able to prepare the nucleotide sequence of claim 2 and the fragments set forth in new claims 44-46 and 59 using the specification of the present invention and specifically the sequence listing. Therefore, claims 44-46 and 59 are fully enabled by the present specification.

The specification of the present application also enables one of skill in the art to determine if the *chfr* gene is expressed in a cell or if the gene is mutated. The specification clearly teaches that the presence (or absence) of the *chfr* gene or a mutation in the gene is indicative of the cell's susceptiblity to anti-mitotic drugs, such as the Taxol® agent. This is determined by using PCR and fragments of the nucleic acid sequence of SEQ ID NO: 1 that are between 12-30 nucleobases in length, as set forth by the specification. In fact, Applicants provide a representative number of primers that can be used in the present invention and are 12-30 nucleobases in the length (Table 1). Further, no undue experimentation would be necessary to prepare the sequences of the present invention since Applicants have provided the exact nucleotide sequence of *chfr* which is set forth in SEQ ID NO: 1.

The examples of the present invention also provide one of skill in the art to practice the present invention using widely known techniques. For example, the sensitivity of cancer cells to different anti-mitotic drugs, such as the Taxol® agent, was examined in Example 4.

As taught by the specification, normal primary cells and tumor cell lines that express wild-type *chfr* exhibited delayed entry into metaphase when exposed to an agent that disrupts microtubule function and induces mitotic stress. See Example 4 and Fig. 2 of the specification which state that three types of cancer cells that do not express detectable *chfr*, i.e., DLD1, HCT116 and IMR5, showed high mitotic indices in response to exposure to nocodazole for 16 hours. Only one cancer cell line that lacked *chfr* showed the same response. All other cancer cells lacking *chfr* showed low mitotic indices under the same conditions, indicating that they entered metaphase without delay and survive mitotic stress less well than cells expressing *chfr*.

The specification in Fig. 3C further shows U20S and DLD1 cells transiently transfected with plasmids expressing wild-type *chfr* or the inactivating mutant (M580) *chfr* or control cells with no *chfr* (-). After exposure to nocodazole treatment for 16 hours, only those cells expressing the wild-type *chfr* showed low mitotic indices, i.e.,

showed less mitotic stress in response to the treatment. The cells expressing the inactivated *chfr* or no *chfr* at all were much more sensitive to the mitotic stress inducer.

Similarly FIGs. 5-8 show the reaction of cells exposed to nocodazole (Noc) or Taxol (Tx). As described in Example 4, particularly at pages 44-45, cells that express detectable wt *chfr* survive better when exposed to inducers of mitotic stress; whereas cells that do not express detectable *chfr* are more sensitive to such agents.

This evidence demonstrates that the absence of *chfr* expression or its inactivation in cells (e.g., due to mutation in cancer cells), causes those cells to display increased sensitivity to anti-mitotic drugs, such as nocodazole and Taxol.

Applicant's post-filing publication Mariatos et al., Cancer Research, 63:7185-7189 (November 1, 2003) further demonstrates the correctness of Applicant's teachings in the present specification. According to Mariatos, inactivating mutations in the *chfr* gene occur in cancer cells. Such inactivation correlates to higher sensitivity to anti-mitotic drugs. See, Fig. 2 at page 7187 and page 7188 at col. 1, 2nd full paragraph, and the paragraph spanning cols. 1 and 2.

Reconsideration of this rejection is requested.

35 USC § 102(b) Rejection

Claim 2 is rejected under 35 USC § 102 (b) over Boehringer Mannheim Biochemicals, 1994 Catalog, page 93.

The Examiner asserted that Boehringer teaches a kit comprising random primers that encompass all possible 6-nucleotide sequences and that one of skill in the art would be able to prepare Applicants' claimed antisense sequences.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason.

Claim 2 of Applicants' invention is drawn to the full 2679 nucleobase nucleic acid sequence of SEQ ID NO: 1 or a sequence complementary thereto. In contrast, the primers of Boehringer are only 6 nucleic acids in length. Boehringer therefore cannot teach or suggest the ***2679 nucleobase*** nucleic acid sequence of claim 2 of Applicants' invention.

Nor does Boehringer teach or suggest independent claims 21 or 49, and the claims depending therefrom, which provide reagents or kits containing nucleic acid sequences of between ***12-30 nucleobases*** of SEQ ID NO: 1.

Boehringer also does not teach or suggest newly added claim 59 which provides isolated nucleotide sequences that encode portions of the nucleic acid sequence of SEQ ID NO: 2 and that are ***219, 132, 498, or 219 nucleobases*** in length.

Reconsideration of this rejection is requested.

35 USC § 103(a) Rejections

Claims 21-23, and 25 are rejected under 35 USC § 103(a) over Jacobs (International Patent Publication No. WO 00/21991) in view of Sambrook et al. (1989, Molecular Cloning, A Laboratory Manuel, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, p. 10.6-10.7).

The Examiner asserted that it would have been obvious to one of skill in the art to label the nucleic acid of Jacobs using the method of Sambrook for detecting the presence of the nucleic acid sequence for diagnostic purposes.

The Examiner also asserted that it would have been obvious to formulate the polynucleotide sequence of Jacobs as a kit in order to have standardization for tests to characterize the polynucleotide sequence for commercial application.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason.

The cancellation of claims 22 and 25 moots the outstanding rejection as applied to these claims.

Jacobs is drawn to expressed sequence tags (EST) and provides examples of at least 2500 ESTs. SEQ ID NO: 911 of Jacobs is a nucleotide sequence 575 nucleobases in length. As noted by the Examiner, this 575 nucleotide sequence is a fragment of SEQ ID NO: 1 of Applicants' invention. However, Jacobs does not provide any teaching regarding the nature of the fragment, what or if it encodes, and any use therefor.

Specifically, Jacobs does not teach or suggest any nucleic acid sequences (i) 12-30 nucleic acids in length that are complementary or identical to portions of SEQ ID NO: 1 (claims 21 and 49), (ii) the 2679 nucleobase nucleic acid sequence of SEQ ID NO: 1 of

Applicants' invention (claim 2), or (iii) nucleic acid sequences 219, 132, 498, and 219 nucleobases in length as set forth in claim 59 of Applicants' invention.

Further, Jacobs does not discuss using the EST discussed therein for determining expression of the *chfr* gene or a mutation therein. Jacobs therefore cannot teach or suggest the present invention. In fact, since Applicants were the first to (a) identify the *chfr* gene and (b) utilize fragments of the *chfr* gene in PCR for detecting *chfr* in a cell, Jacobs does not teach or suggest Applicants' invention.

The teachings of Sambrook are only general teachings regarding detecting the presence of nucleic acid sequences. Sambrook adds nothing to Jacobs to teach or suggest nucleic acid sequences 12-30 nucleic acids in length and complementary to SEQ ID NO: 1 that are useful for detecting the expression of or a mutation in the *chfr* gene.

No combination of Jacobs of Sambrook teaches or suggests the sequences, reagents, or kits of Applicants' invention which teach detecting the expression of or a mutation in the *chfr* gene and correlating the same with the sensitivity of a subject to anti-mitotic drugs, such as the Taxol® agent. With respect, Applicants submit that the Examiner is improperly using hindsight to construct the outstanding obviousness rejection, and has failed to interpret the prior art as a whole, from the point of view of a person having ordinary skill in the art at the time the invention was made, as required by 35 USC § 103.[1]

An obviousness rejection cannot be made by combining documents to make the bald suggestion that it is "obvious to try" to make the full-length *chfr* nucleotide sequence, fragments of the *chfr* gene that are 12-30 nucleobases in length, or the specific fragments of claim 59 of the present invention simply because others have made nucleotide sequences that are considerably larger than 30 nucleobases in length that overlap with a portion of the full-length sequence of the *chfr* gene. Nor is it "obvious to try" to use the same to determine if *chfr* is expression or mutated in a cell. The US patent

[1] "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art of deprecate the claimed invention" In re Fine, 837 F. 2d 1081, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988)

law has long held that the "obvious to try" standard is not the appropriate standard for a determination of patentability.

If one were to use the teachings of Sambrook to utilize the nucleic acid sequences set forth in Jacobs in PCR, one would still not contemplate Applicants' invention. This teaching is only provided by Applicants' specification. The mere fact that Jacobs and Sambrook may be modified in the manner as suggested by the Examiner does not make the modification obvious, unless these documents suggested the desirability of the modification.[2] As discussed above, these documents in combination and taken as a whole[3] do not suggest the claimed invention.

Reconsideration of this rejection is requested.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

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2 *In re Fritch*, 23 USPQ2d 1780, 1783-1784 (Fed. Cir. 1992), citing *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

3 *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 837 F. 2d 1044, 5 USPQ2d 1434, 1438 (Fed. Cir. 1988) "Something in the prior art as a whole must suggest the desirability, and thus the obviousness, of making the combination."